

rats. They implanted the animals with adjustable electrodes targeting the CA3 and CA1 subregions of the hippocampus, areas in which place-related firing is robust and well characterized. The rats were trained to run around a square track for chocolate wafer rewards, and neural data were collected both during rest sessions in the animals' home cages and run sessions on the track. During the rest between two run periods, either LTP-inducing stimulation or low-frequency control stimulation (LFS) was delivered to the ventral hippocampal commissure (VHC), a fiber bundle of projections to CA3 and CA1. The place-related firing of individual cells was then analyzed during run sessions before and after LTP/LFS. Test stimuli delivered to the animals during rest periods allowed the authors to assess the degree of potentiation at each recording site, measured as a change in the slope of stimulus-triggered EPSPs in the local field potential at each electrode tip.

Dragoi et al. found that LTP induction changed the hippocampal place responses without disrupting characteristic network features. The degree of LTP correlated with the degree of change in place-related firing such that LTP produced much greater potentiation at some recording sites than at others, and neurons recorded from sites with greater potentiation were more likely to change their place representations. These new representations involved shifts of the original field, loss of the field, or appearance of a new field. The new place fields were indistinguishable from the endogenous representations: place fields of the changed cells were similar to the original fields in size and shape; the average firing rate of the population did not change; and characteristic small time scale correlations of the hippocampal ensemble were preserved. LTP-induced place firing showed the directional specificity typical of place cells (McNaughton et al., 1983), such that a new field might appear when the animal traveled clockwise around the track but not counterclockwise. They also fired with a normal relationship to the theta rhythm, a 4–12 Hz oscillation observed in the hippocampal EEG of awake behaving rats.

There was, however, an important difference between the LTP-driven place representation and the animal's own place representation: permanence. Once a rat forms a place map (a process that is well underway after 10 or so minutes of exploring a new spot [Wilson and McNaughton, 1993]), each neuron's place response is generally stable for as long as the neuron can be recorded (Thompson and Best, 1990). In contrast, the place responses generated by LTP disappeared as the potentiation faded over a period of about 6 hr. This result is quite elegant, as it strongly suggests a causal relationship between LTP and place cell coding, but it leaves the question: if an LTP-like mechanism is driving place field formation, what signal maintains the changed synaptic weights across days and weeks? Or in the parlance of the hippocampal community, how are changes in synaptic weights "consolidated"?

One possibility is that synaptic changes are consolidated when the animal is in a particular attentional state, such as when it perceives an experience as novel. Hippocampal consolidation requires protein synthesis (McGaugh, 2000), and it may be that protein synthesis is triggered by a systemic learning/novelty/error signal.

In this case, we would predict that the place representation driven by Dragoi et al. would have been permanent if it were generated when the animal was in a novel place.

Dragoi et al.'s findings provide an important link between the cellular processes associated with synaptic plasticity and the hippocampal representation of space. The authors showed that altering the synaptic weights in the hippocampal network correspondingly alters the hippocampal representation of space without disrupting the network dynamics. This strong connection between long-term potentiation and modification of the hippocampal place code outlines a possible causal relationship between plasticity and spatial memory.

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Can't Learn without You: Predictive Value Coding in Orbitofrontal Cortex Requires the Basolateral Amygdala

Basolateral amygdala and orbitofrontal cortex are implicated in cue-outcome learning. In this issue of *Neuron*, Schoenbaum et al. show that, following basolateral amygdala lesions, cue-selective neurons in orbitofrontal cortex are more sensory driven and less sensitive to the motivational value of an outcome, suggesting that predictive value coding in orbitofrontal cortex is dependent on input from basolateral amygdala.

In order to survive, most animals require the ability to predict when and where in the environment rewarding or punishing stimuli will occur and adapt behavior accordingly. Research in affective neuroscience over the

past 30 years has implicated a number of key regions in the mammalian brain in this form of learning. These include the amygdala in the medial temporal lobes, orbitofrontal cortex on the ventral surface of the frontal lobes, dopaminergic centers in the midbrain, and the ventral striatum in the basal ganglia. Much is now known about the segregated functions of each of these areas. However, these regions do not exist in isolation. Rather, they constitute a network of highly interconnected brain areas specialized for affective processing. Arguably, the neural substrates of complex affective behavior can only truly be understood as a product of the interactions or "functional integration" within this network (Friston, 2002). In the current issue of *Neuron*, Schoenbaum and colleagues report one of the first studies to provide an insight into the nature of the interactions between two of these regions: orbitofrontal cortex and the basolateral complex of the amygdala.

Orbitofrontal cortex (OFC) has long been implicated in affective behavior. Damage to this area in humans is associated with personality changes and impairments in everyday decision making (Damasio and Van Hoesen, 1983). Neuropsychological investigations in rats, nonhuman primates, and humans have revealed a role for this region in the flexible control of goal-directed behavior that may underpin such overt behavioral changes. Specifically, OFC lesions appear to result in difficulties in adapting behavior on the basis of prior rewarding and punishing feedback. This has been shown using tasks such as visual discrimination reversal in which two stimuli are presented and the animal is required to choose between them. One of the stimuli is followed by a reward and the other by nonreward. Over time, the animal learns to choose the stimulus associated with reward and avoid the nonrewarded stimulus. Once the animal has learned to do this, the contingencies are reversed so that the previously rewarded stimulus is no longer rewarded and the previously unrewarded stimulus is now rewarded. In contrast to intact animals, those with OFC lesions have difficulty altering their behavior following a change in contingencies and persist in choosing the previously rewarded stimulus (Dias et al., 1996). Humans with OFC lesions have also been found to be impaired at reversal learning, as well as at more complex affective decision-making tasks in which, in order to optimize their total winnings, they must choose advantageously from a series of choices that yield differing quantities of rewarding and punishing feedback (Rolls, 2000; Bechara et al., 2000).

Some evidence is now beginning to emerge as to the nature of underlying neuronal activity in OFC that may mediate such functions. Single-unit neurophysiology studies have revealed that neurons in this region respond to rewarding stimuli in different modalities and that some OFC neurons are sensitive to the current motivational value of such rewards (Rolls, 2000). Importantly, neurons have been found in this region that respond to stimuli predictive of subsequent rewards and punishments or during a delay period in which a reward is expected (Schoenbaum et al., 1998; Tremblay and Schultz, 2000). Furthermore, some OFC neurons flexibly alter their responses following a reversal in reinforcement contingencies in that they cease responding to the previously rewarded stimulus and in some cases

begin responding to the newly rewarded stimulus (Rolls, 2000). These studies suggest that OFC is involved in maintaining an active representation of which stimuli in the environment are predictive of reward and punishment and flexibly adapts such representations with respect to changes in reinforcement contingencies.

How do OFC neurons come to represent this reward-predicting information? Is it computed within OFC itself, or does the information enter OFC from another part of the reward network? One candidate region for the latter possibility is the basolateral complex of the amygdala (ABL), a region composed of basal, lateral, and accessory nuclei which are a subset of over 15 distinct subnuclei in the amygdala. One of the distinguishing anatomical characteristics of this region is that it has prominent reciprocal connections with OFC and is the main source of amygdala inputs to OFC (Carmichael and Price, 1995). Recent evidence suggests that somewhat analogous to the effects of OFC lesions, damage to ABL results in difficulty in flexibly adapting behavior in the light of changes in reward value of the associated outcome. For instance, if an intact animal has learned to press a lever for reward and the value of that specific reward is then decreased by feeding the animal to satiety on that food, then the animal will subsequently decrease its rate of responding on the lever associated with the satiated food. Animals with ABL lesions do not adapt their behavior in this way. Instead they maintain responding on the lever even though the outcome has been devalued (Malkova et al., 1997). It has been argued on the basis of these and other findings that ABL is involved in enabling a predictive cue to gain access to the current reward value of the associated rewarding or punishing stimulus (Cardinal et al., 2002).

To address the role of ABL in the coding of predictive reward within OFC, Schoenbaum et al. (2003) performed selective ABL lesions in one group of rats and sham control lesions in another and then recorded from single OFC neurons during performance of a reward learning task. In this task, the rat had to sample from an odor port, which then triggered the delivery of one of two odors. After sampling the odor, the rat could then decide to sample a rewarding or aversive taste from a fluid well (GO response) or not (NO-GO response). The gustatory stimulus could either be a rewarding sucrose solution or else an aversive quinine solution. Critically, the odor cue sampled at the beginning of the trial was informative as to which solution the rat would obtain if a GO response was performed. After the intact control rats finally learned to avoid choosing the GO response on trials in which the aversive stimulus was cued, a group of neurons in OFC were found to have specific responses to the olfactory cues in that some neurons responded to the cue predicting reward, and another group of neurons responded to the cue predicting the aversive solution. In ABL lesioned rats, these neurons were also present but were fewer in number.

Even before rats had learned to perform appropriate behavioral responses, a population of OFC neurons was found to respond in anticipation of the outcome. That is, they responded selectively during the delay period after the response had been made but before the outcome was delivered. In intact rats, a subset of these neurons went on to develop specific responses to the

cue stimuli. Such learning-related changes were notably absent in the ABL lesion group. Although outcome-expectant OFC neurons were present in this group during learning, very few of these neurons went on to develop cue-specific responses. Thus, ABL lesions abolished acquisition of cue-specific responses in a subpopulation of outcome-expectant OFC neurons.

It is possible that neurons with specific responses to the predictive cues are actually indifferent to the affective value of the associated outcome and merely respond to the identity of the cue itself. To test this possibility, Schoenbaum et al. reversed the contingencies so that the cue previously associated with reward was now associated with the aversive outcome and vice versa. If at least some of these neurons are able to change their responses in that they cease responding to the previously rewarded stimulus, this would provide evidence that the neurons do in fact code for the motivational significance of the outcome. In control animals, the majority of such neurons ceased responding to the odor cue for which they were previously selective, whereas a smaller number of cue-selective neurons actually reversed their odor-specific responses after reversal. This shows that, in the control group, cue-selective neurons do indeed code for the affective significance of the outcome as they alter their responses following a change in the reinforcement contingencies. The situation was markedly different in the ABL lesion group. In this group, a significantly greater proportion of cue-selective neurons did not change their responses as a function of reversal, indicating that they are insensitive to changes in the reward value of the associated outcome. Some of these neurons did not modify their cue-specific responses at any stage during learning, suggesting that they may code sensory aspects of the olfactory cue rather than the associated reward value of the outcome.

It is interesting to note that the ABL group were unimpaired at acquisition of the go/no-go responses in spite of their impoverished OFC representations (though they were mildly impaired at the subsequent reversal). This might be taken to suggest that actually the ABL does not contribute behaviorally significant information to OFC during instrumental conditioning. However, as the authors point out, ABL lesions do not necessarily produce impairments at initial acquisition of instrumental responses for reward. This may be because such a task can be accomplished through a number of different mechanisms, some of which do not require knowledge of the current value of the associated outcome, such as stimulus response learning. Lesions of ABL or OFC are known to produce impairments on tasks that do require knowledge of current outcome values. One such task is the reinforcer devaluation procedure described earlier, in which animals make instrumental responses to gain access to a reward that is subsequently devalued by feeding to satiety. Indeed, in one of the few other studies to date to investigate interactions between the amygdala and OFC, Baxter and colleagues showed that crossed-unilateral lesions of amygdala in one hemisphere and OFC in the other produced impairments at adapting behavior following a decrease in the reward value of an outcome, indicating that these areas do need

to interact in order to support at least some types of affective behavior (Baxter et al., 2000).

The current study by Schoenbaum et al. marks an important first step in characterizing interactions between components of the reward system. It provides evidence that ABL lesions do have substantial effects on neural representations of predictive value in OFC. It is clear that these two brain regions do interact during learning and that, without input from the ABL, predictive value coding in OFC becomes somewhat more impoverished and less adaptive. The study provides an elegant illustration that the neural substrates of affective behavior are best understood as the product of functional integration between multiple brain areas.

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